Prolonged Intrahepatic Cholestasis and Renal Failure Secondary to Anabolic Androgenic Steroid-Enriched Dietary Supplements

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Abstract: The illegal enrichment of anabolic androgenic steroids in over-the-counter dietary supplements is well documented, but the health consequences have not been widely recognized. Three recent reports document cholestatic jaundice and nephropathy due to these compounds. We present 3 additional cases of anabolic androgenic steroid-enriched dietary supplement-induced hepatotoxicity and 1 case of renal failure, and we review the literature and the relevant features of this growing health concern. Recognition of this entity could obviate the need for invasive diagnostic testing and hospitalization and facilitate diagnosis and appropriate counseling.

Key Words: anabolic steroids, cholestasis, drug-induced liver injury, hepatotoxicity, renal toxicity, dietary supplements, nutritional supplements, jaundice, medical ethics

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Following the 1934 synthesis of testosterone[1] came the development of synthetic steroid derivatives, a period termed as "The Golden Age of Steroid Chemistry."[2] The abuse of anabolic androgenic steroids (AAS) by bodybuilders and athletes[3–7] led to the Anabolic Steroids Control Act of 1990, rendering these compounds class III controlled substances.[8–11] That AAS are routinely added to over-the-counter dietary supplements is now well substantiated.[2–4,6,8,12–16] Judkins et al[17] recently confirmed that approximately one-quarter of the 58 dietary supplement samples purchased from retail outlets and internet sites in the United States showed the presence of low levels of steroid and/or stimulant contamination that were not declared on the label. As AAS are controlled substances, such enrichment is illegal. The identification of off-label anabolic steroids and other illegal stimulants in over-the-counter dietary supplements is a relatively recent phenomenon.[18]

To date, reports of any deleterious health consequences of purportedly low doses of AAS in dietary supplements are scant; documentation of clinical disease states caused by AAS-enriched dietary supplements raises medicolegal issues and governmental oversight health concerns. Three recent case reports of AAS-induced cholestatic jaundice, including 1 case of IgA nephropathy[8,12] highlight the consequences of dietary supplements that contain AAS. We present 3 additional cases of AAS-induced hepatotoxicity, including 1 case of AAS-induced renal injury, now doubling the number of reported cases within the past year. In addition, we review the salient features of this growing phenomenon.

PATIENT 1

A 21-year-old previously healthy white man presented with nausea, anorexia, jaundice, and pruritus (Table 1). He denied alcohol consumption or illicit drug use and took no prescription medications on a regular basis but did acknowledge use of the over-the-counter supplement Superdrol, a bodybuilding agent containing methasteron,[19] for several months before his presentation. He had purchased this compound over the internet, and he discontinued taking the supplement at the onset of his symptoms. His aminotransferases and alkaline phosphatase were elevated at initial presentation and the total bilirubin was 9.9 mg/dL (Table 2). An ultrasound showed a normal common bile duct with no evidence of cholelithiasis.

Physical examination revealed marked scleral icterus, jaundice, and a soft nontender abdomen with no organomegaly. He had no stigmata of chronic liver disease. An evaluation for viral hepatitis was negative. Iron studies, ferritin, α-1 antitrypsin, ceruloplasmin, and an autoimmune liver screen were all normal or negative.

Two weeks later, his pruritus worsened, and total bilirubin was now 38.9 mg/dL. He was started empirically on oral prednisone, 40 mg/d with tapering over the next several weeks. One month later, the bilirubin remained high at 31.8 mg/dL and on follow-up 6 weeks later, the bilirubin was 2.3 mg/dL, coinciding with clinical improvement.

PATIENT 2

A previously healthy 30-year-old white businessman initially presented to an outside hospital with a 5-week history of jaundice and pruritus (Table 1). His medications included omeprazole and herbal supplements including chondroitin sulfate, glucosamine, glutamine, and creatine. He also acknowledged the use of a bodybuilding supplement that contained dehydroepiandrosterone. Concerned about his symptoms, he stopped consuming this supplement just before his hospitalization.

An ultrasound showed no biliary dilation and a normal liver. Markers for viral and autoimmune hepatitis were negative and serum ceruloplasmin level was normal.

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TABLE 1. Clinical Presentation of Anabolic Androgenic Steroid-Enriched Supplement-Induced Liver Injury: Signs and Symptoms*

	Present Series			Cases From the Literature		
	Patient 1	Patient 2	Patient 3	Patient 4[8]	Patient 5[9]	Patient 6[9]
Pruritus	+	+	+	+	+	+
Jaundice	+	+	+	+	+	+
Scleral icterus	+	+	+	+	+	+
Hepatomegaly	−	−	−	−	+	−
Splenomegaly	−	+	−	−	−	−
Fever	−	−	−	−	−	−
Malaise	−	−	+	−	+	+
Nausea	+	−	+	+	Unknown	Unknown
Vomiting	+	−	−	+	Unknown	Unknown
Weight loss	−	−	+	+	+	+
Abdominal discomfort	−	−	−	+	−	−
Pale stools	Unknown	+	+	+	Unknown	Unknown
Dark colored urine	+	+	+	+	Unknown	Unknown

*+, present; −, absent.

A magnetic resonance cholangiopancreatography was unremarkable. He was sent home on hydroxyzine and cholestyramine for symptom relief.

Five weeks later, he followed-up in the Hepatology clinic to confirm resolution of his symptoms; he made an uneventful recovery. During the course of his illness, his total bilirubin peaked at 8 mg/dL, and then declined. His aminotransferases and alkaline phosphatase were raised with a peak alanine aminotransferase of 200 IU/L and an alkaline phosphatase twice the upper limit of normal. His laboratory values are summarized in Table 2.

PATIENT 3

A 38-year-old previously healthy white man initially presented for evaluation of jaundice (Table 1). He first noticed the onset of scleral icterus 6 weeks previously. His symptoms included intense and worsening pruritus, generalized fatigue, nausea, decreased energy, and weight loss.

His past history was unremarkable. He denied alcohol or illicit drug use and used no prescription medications. Further questioning revealed the use of M-Test 2, a bodybuilding nutritional supplement, which he started 14 weeks previously. He consumed a total of 57 tablets until 5 weeks before presentation. A review of the ingredients of M-Test 2 indicates the presence of 17α-methyl-etioallocholan-2-ene-17β-01.[20]

Physical examination revealed deep scleral icterus and jaundice. His abdomen was soft and nontender and without organomegaly. He had no stigmata of chronic liver disease. His total bilirubin was 10 mg/dL. His aspartate aminotransferase and alanine aminotransferase were 199 and 467 IU/L, respectively. His creatinine was 1.9 mg/dL from a baseline of 1.2 mg/dL (Table 2). Tests for viral hepatitis were negative. Tests for autoimmune liver screen were negative and serum protein electrophoresis, iron studies, ferritin, and ceruloplasmin levels were normal. Over the next several weeks, his total bilirubin rose to 35 mg/dL.

Owing to worsening of his symptoms and renal failure, he was admitted to the hospital. A transjugular liver biopsy showed extensive canalicular cholestasis with mild to moderate periportal chronic inflammation and focal

TABLE 2. Clinical Presentation of Anabolic Androgenic Steroids-enriched Supplement-induced Liver Injury: Demographics, Dietary Supplements, and Laboratory Values

	Present Series			Cases From the Literature		
	Patient 1	Patient 2	Patient 3	Patient 4[8]	Patient 5[9]	Patient6[9]
Age (in years)	21	30	38	23	40	31
Sex	Male	Male	Male	Male	Male	Male
Ethnicity	White	White	White	Hispanic	African American	White
Hospital admission	Yes	Yes	Yes	Yes	Yes	Yes
Dietary supplement	Superdrol	Dehydroepiandrosterone	M-Test 2	Superdrol	Superdrol	Unknown
Cumulative dose	Unknown	Unknown	57 tablets	720 mg	840 mg	Unknown
Time from initial ingestion to presentation (in weeks)	≥4	Unknown	8	2.5	6	8
Time from presentation to resolution (in months)	3	3	2.5	1	2.5	3.5
Peak total bilirubin (mg/dL)	38.9	8	53.8	42	49.7	43.7
Peak aspartate aminotransferase (IU/L)	124	50	199	71	121	55
Peak alanine aminotransferase (IU/L)	256	200	467	104	301	59
Peak alkaline phosphatase (IU/L)	250	104	494	280	416	375
Peak creatinine (mg/dL)	1.6	1.2	2.4	3.4	3.2	Unknown
Resolution of symptoms	Yes	Yes	Yes	Yes	Yes	Unknown

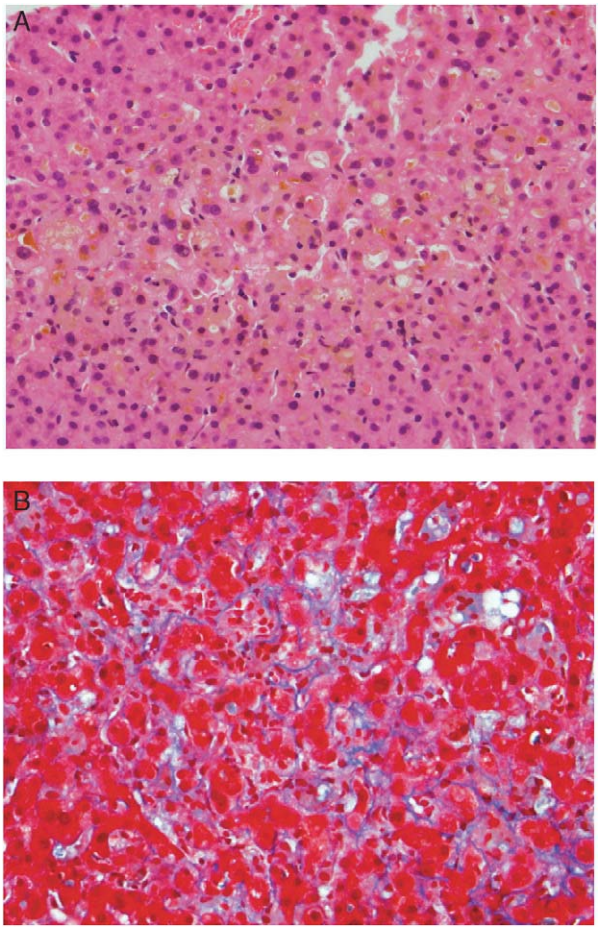

FIGURE 1. A, Liver histology demonstrating canalicular cholestasis, periportal inflammation (hematoxylin and eosin, ×400) and (B) focal fibrosis consistent with anabolic steroid-induced cholestasis (trichrome, ×400).

fibrosis (Fig. 1). Table 3 shows the liver biopsy findings in the 6 patients reported to date.

His serum creatinine rose to 2.4 mg/dL and he was evaluated by Nephrology. A renal ultrasound did not explain his acute renal failure and hydration resulted in no improvement in renal function. He was discharged on oral hydroxyzine and ursodiol, and when seen 3 weeks later, he remained deeply jaundiced with a serum bilirubin of 32 mg/dL. He was started on oral prednisone, 40 mg/d with a slow taper, and jaundice abated and renal function normalized over the next 2 months.

DISCUSSION

Anabolic steroid-induced liver injury includes peliosis hepatitis, various benign and malignant neoplasms, and cholestasis.[21] The jaundice may be prolonged, and may lead to nephropathy.[12] The US Food and Drug Administration (FDA) classified these compounds as class III controlled substances in 1990, limiting their use to specific indications such as replacement of male sex steroids in men who have androgen deficiency, treatment of certain rare forms of aplastic anemia, and the counteraction of catabolic states such as trauma or HIV wasting.[22]

TABLE 3. Liver Histology in Anabolic Androgenic Steroids-enriched Supplement-induced Liver Injury: Signs and Symptoms*

	Present Series			Cases From the Literature		
	Patient 1	Patient 2	Patient 3	Patient 4[8]	Patient 5[9]	Patient 6[9]
Ductal injury	ND	ND	−	−	−	−
Portal or periportal inflammation	ND	ND	+	+	+	+
Parenchymal injury	ND	ND	−	−	−	+
Vanishing bile duct syndrome	ND	ND	−	−	−	−
Cholestasis	ND	ND	+	+	+	+
Fibrosis	ND	ND	+	−	−	+

*+, present; −, absent.
ND indicates not done.

The presence of AAS in dietary nutritional supplements is not widely appreciated and recently made national headlines with the observation, "clearly…either the laws are not there or they're not being enforced."[18] Several published reports over the past year[3,6,13–16] have unequivocally demonstrated the presence of AAS in food products sold as nutritional supplements (Table 4). Van Poucke et al[16] used liquid chromatography-tandem mass spectrometry to confirm the presence of AAS in dietary supplements. Parr et al[14] showed high amounts of 17-methylated AAS in dietary effervescent tablets. Baume et al[13] showed the presence of these compounds in various dietary supplements.

Nevertheless, until recently, the hepatotoxicity of these legally purchased nutritional supplements has not been appreciated. Jasiurkowski et al[12] and Kafrouni et al[8] recently described 3 patients who developed profound cholestasis after the ingestion of over-the-counter nutritional supplements containing anabolic steroids. In addition, Jasiurkowski et al[12] also described a single case of IgA nephropathy resulting from AAS-enriched dietary supplements. The presently reported 3 additional hepatotoxicity cases now yield 6 such cases within the past year, including 2 cases of renal failure. Outstanding uncertainties include whether such hepatotoxicity is dose related or idiosyncratic, and whether other potential hepatic or renal consequences of these dietary supplements may occur.

The FDA is responsible for the monitoring of safety information of regulated substances, but has limited jurisdiction over the distribution of health food supplements; the Center for Food Safety and Applied Nutrition is responsible for the agency's oversight of these products,[24] and the Federal Trade Commission regulates dietary supplement advertising.[25]

TABLE 4. Anabolic Steroids Found in Each of the Nutritional Supplements Ingested[19,20,23]

Nutritional Supplement	Anabolic Androgenic Steroid
Superdrol	Methasteron
Halodrol	A steroid that resembles oral-turinabol
M-Test 2	17α-methyl-etioallocholan-2-ene-17β-01

A recent letter from the director of Office of Compliance at the Center for Food Safety and Applied Nutrition warned the makers of Anabolic Xtreme Superdrol that the presence of methasteron classified this compound as a regulated drug rather than a dietary supplement. The letter further stated that as Anabolic Xtreme Superdrol is not an FDA-approved drug, it cannot be marketed in the United States, and that continued distribution violates the law.[26] Despite the warning, however, the product remains widely available over the internet.[19,20,23]

The use of corticosteroids to treat drug-induced cholestasis remains controversial. On the basis of our prior favorable experience using prednisone to treat a case of prolonged anabolic steroid-induced cholestasis[27] and given his unremitting jaundice and clinical deterioration, we elected to try an empiric course of steroids in our third case. Our anecdotal experience would once again suggest a potentially salutary role for the use of corticosteroids in this setting.

The rapid reporting of several cases of AAS-induced liver injury from dietary supplements emphasizes the growing emergence and importance of this condition and the need for clinicians to become aware of the sequelae of jaundice and renal failure, especially among young men who are unknowingly consuming hepatotoxic agents. Knowledge of this entity could obviate the need for invasive or expensive diagnostic testing and hospitalization and facilitate diagnosis and appropriate counseling.

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